REMARKS

Status of Claims and Amendment

Upon entry of the amendment, which is respectfully requested, claims 1, 3-5, 9-10, 14, 16, 19 and 23 will be amended. Claims 2, 13, and 24-25 will be canceled. Claim 18 has been canceled. New claims 26 and 27 will be added. Claims 1, 3-12, 14-17, 19-23, and 26-27 are all the claims pending in the application.

Claims 1, 19, and 23 have been amended to recite "orally" and to remove "prophylaxis." Support for this amendment to claims 1, 19, and 23 may be found at least at page 5, lines 8-9 and page 6, last paragraph of the present specification. In addition, claim 23 has been amended to replace "corresponds to a portion of the structure of" with "derived from."

Claims 3, 4, 14, and 16 have been amended to change the claim dependencies to be consistent with the other amendments to the claims.

Claim 5 has been amended to remove "totally or partially."

Claims 9 and 10 have been amended to correct for grammatical and typographical errors.

Claim 12 has been amended to recite that the "polysulphated polysaccharide [is] selected from the group consisting of inulin polysulphate, gellan polysulphate, pullulan polysulphate, curdlan polysulphate, alginic acid polysulphate, laminarin polysulphate, and pectin polysulphate." Support for the amendment to claim 12 may be found at least at page 4, lines 18-24 of the present specification.

No new matter is added.

Claim of Priority

The Examiner has not acknowledged Applicants' claim to foreign priority or receipt of Applicants' foreign priority document, namely P200400464.

Applicants note that according to PAIR, the priority document was filed on August 23, 2006. Accordingly, Applicants respectfully request that the Examiner acknowledge Applicants' claim to foreign priority as well as receipt of Applicants' foreign priority document in the next Office communication.

Withdrawn Objections/Rejections

1. Applicants thank the Examiner for withdrawal of the objection to the specification.

2. Applicants thank the Examiner for withdrawal of the rejection to claims 1-25 under 35 U.S.C. § 101.

3. Applicants thank the Examiner for withdrawal of the to claims 1-25 under 35 U.S.C. § 112, second paragraph.

Response to Rejections Under 35 U.S.C. § 112

1. Enablement

At page 3 of the Office Action, the Office Action rejects Claims 1-17 and 19-25 under 35 U.S.C. § 112, first paragraph, as lacking enablement.

The Office Action appears to assert that while the specification is enabling for the treatment of osteoarthritis, the specification is not enabling for the method of prophylaxis of osteoarthritis. The Office Action asserts that the ordinary dictionary meaning (Dictionary.com) of the term prophylaxis is prevention of a disease, and Applicants have not provided a different

definition for the term prophylaxis. The Office Action asserts that one of ordinary skill in the art would not extrapolate the results of the instant examples to the prevention of osteoarthritis using the active agent as instantly claimed.

In response, Applicants note that because osteoarthritis is a disease that affects the majority of the persons from 65 years of age, and persons that have suffered a traumatism, it is important to prevent the disease or at least to postpone its emergence.

Bearing in mind that the resistance and capacity of repair of the cartilage is determined by the aggrecans, Applicants note that Example 1A demonstrates the efficiency of inulin polysulphate in the prophylaxis of osteoarthritis. Specifically, Example IA describes the *in vitro* effect of inulin polysulphate sodium salt on the synthesis of aggrecans using human articular chondrocytes (obtained post mortem) in the absence of a catabolic stimulator. In the Tables of Example IA, inulin polysulphate sodium salt is shown to induce an increase in the production of aggrecans in the interterritorial matrix (Table 1), an increase in the production of aggrecans associated with the cells (Table 2), as well as an increase in the total production of re-synthesized aggrecans (Table 3). Thus, one of ordinary skill in the art would interpret the data in the specification as sufficient evidence that osteoarthritis can be prevented by administration of the sulphated and polysulphated polysaccharides.

In this regard, one of ordinary skill in the art would be enabled, based on the guidance in the specification, to practice the method of new claims 26-27 for the prophylaxis of osteoarthritis comprising administering orally inulin polysulphate.

Nevertheless, and solely to advance prosecution of the present application, claims 1, 19, and 23 have been amended to remove "prophylaxis."

Claims 2, 13, and 24-25 have been canceled. Accordingly, the rejection is rendered moot with regard to claims 2, 13, and 24-25.

Reconsideration and withdrawal of the rejection under § 112, first paragraph, is respectfully requested.

2. Indefiniteness

Claims 5, 9-11 and 23 are rejected under 35 U.S.C. § 112, second paragraph, as being allegedly indefinite.

The Office Action alleges that the term "partially" in Claim 5, and the phrase "portion of the structure" in Claim 23 are relative in nature. The Office Action also notes that the phrase "on anhydrous base" in Claims 9-10 does not make sense.

In response, Applicants note that the claims prior to the present amendment clearly reflects what Applicants consider to be the claimed invention. However, solely to advance prosecution of the present application, the following amendments to the claims have been amend.

With respect to claim 5, the term "totally or partially" has been deleted.

With respect to claim 23, the phrase "whose structure corresponds to a portion of the structure" has been replaced with "derived from", which is the art recognized way to identify synthetic polysulphated polysaccharides.

With respect to claims 9 and 10, the phrase "on anhydrous base" has been amended to recite "on an anhydrous basis."

Reconsideration and withdrawal of the rejection under § 112, second paragraph, is respectfully requested.

Response to Rejections Under 35 U.S.C. § 103(a)

At page 7 of the Office Action, the Office Action rejects Claims 1-17 and 19-25 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Cullis-Hill *et al.* (U.S. Patent No. 5,145,841) in combination with Dictionary.com (2002, page 3), and Komai *et al.* (International Journal of Biological Macromolecules, 2002, 30, 197-204).

The Office Action asserts that Hill *et al.* teach that salts of polysulphated polysaccharides derived from alginic acid, pectin and inulin, are useful for treatment of arthritis.[1] However, the Office Action admits that Hill *et al.* do not exemplify the treatment of osteoarthritis using the polysulphated polysaccharides as instantly claimed. Rather, Hill *et al.* teach treatment of osteoarthritis with metallo complexes of polysulphated polysaccharides.

Further, the Office Action asserts that Komai *et al.* teach a connection between the sulphated polysaccharide, gellan-sulfate, and rheumatoid arthritis. However, the Office Action admits that Komai *et al.* do not specifically teach or exemplify the use of gellan-sulfate for the treatment of arthritis.

Finally, the Office Action cites Dictionary.com as evidence that both rheumatoid and osteoarthritis involve degradation of bone joints, and the Office Action seems to assert that since both rheumatoid and osteoarthritis involve degradation of bone joints, one of ordinary skill in the art would expect that the same compounds would treat both types of arthritis.

Accordingly, the Office Action concludes that one of ordinary skill in the art would readily substitute the polysulphated polysaccharides mentioned by Hill *et al.* as useful to treat

[1] Although the Office Action states that Hill *et al.* teach that the polysulphated polysaccharides are useful to treat "osteoarthritis," Applicants believe that this is incorrect, since Hill *et al.* only teach that the metallo complexes of polysulphated polysaccharides are useful to treat osteoarthritis.

arthritis for the metallo complexed polysulphated polysaccharides employed by Hill *et al.* and expect to treat osteoarthritis. The Office Action also concludes that one of ordinary skill in the art would readily substitute the sulphated polysaccharides of Komai *et al.* for the metallo complexes of polysulphated polysaccharides of Hill *et al.* and expect to treat osteoarthritis.

The Office Action also asserts that sulphated polysaccharides, polysulphated polysaccharides and metallo complexes of polysulphated polysaccharides are structurally similar. Thus, the Office Action asserts that one of ordinary skill in the art would expect sulphated polysaccharides and polysulphated polysaccharides to have the same activity as metallo complexes of polysulphated polysaccharides. Accordingly, the Office Action concludes that sulphated polysaccharides and polysulphated polysaccharides would be expected to be useful to treat osteoarthritis.

In response, Applicants note that the rejection is inapt and that the cited references, taken alone or in combination, fail to render the claimed invention obvious.

First, the Office Action has failed to demonstrate why a person having ordinary skill in the art would have been motivated to combine the references in the manner asserted. Komai *et al.* teach the role of gellan-sulfate in the direct removal of [EDA(+)] fibronectin from the blood of rheumatoid arthritis patients in whom cryogelation occurs in the presence of heparin. Komai *et al.* do not teach the effect of gellan-sulfate on the IL-1 mediated degradation of cartilage as disclosed in Hill *et al.* Consequently, one of ordinary skill in the art would not have reasonably been led to combine the references in the manner asserted by the Office Action.

Furthermore, the Office Action's assertion that since both rheumatoid and osteoarthritis involve degradation of bone joints, it is expected that the same compounds would treat both types of arthritis, is incorrect. In view of the document attached in the Response filed

July 25, 2008, it is clear that osteoarthritis and rheumatoid arthritis are different diseases. Furthermore, it is known in the art that rheumatoid arthritis is a **systemic** inflammatory disease, and is very different from osteoarthritis which is a degenerative condition where the inflammation is limited to joints.

In addition, Applicants note that osteoarthritis and rheumatoid arthritis are two different illnesses for at least the following reasons:

1. In the "Dictionary.com" document cited by the Office Action, osteoarthritis is defined as a disease characterized by the chronic degeneracy of the cartilage of the joints, whereas rheumatoid arthritis is defined as a chronic autoimmune disease. Thus, as evidenced by the Office Action's own document, osteoarthritis and rheumatoid arthritis are two different illnesses.

2. Bioiberica's Medical Report that was provided with the Amendment filed July 25, 2008 clearly describes the differences that exist between osteoarthritis and rheumatoid arthritis.

3. "Martindale - The extra Pharmacopoeia", see pages 11-13, edited by James E.F. Reynolds, Royal Pharmaceutical Society, London, 1996 (attached herewith)[2], explains the characteristics of both diseases. In Martindale, it is clearly stated that the inflammation in osteoarthritis appears in advanced stages of the disease, and is of a different nature than the inflammation that appears in rheumatoid arthritis. Moreover, inflammation in osteoarthritis generally only plays a minor role in the characteristics of the disease, whereas rheumatoid arthritis is characterized principally by a synovial inflammation. Here again, it is clearly

[2] In accordance with M.P.E.P. § 609.05(c), the documents cited herein in support of Applicants' remarks are being submitted as evidence directed to an issue raised in the Official Action, and no fee pursuant to 37 C.F.R. 1.97 or 1.98, or citation on a FORM PTO/SB/08A & B is believed to be necessary.

demonstrated that osteoarthritis and rheumatoid arthritis are two different illnesses which require different therapies.

Accordingly, the presently claimed method for the treatment of osteoarthritis would not have been obvious to one of ordinary skill in the art at the time the invention was made since rheumatoid arthritis and osteoarthritis are two different illnesses, which have different etiologies and require different therapies.

Further, one of ordinary skill in the art would not have had a reasonable expectation of success in obtaining the claimed invention by using the gellan-sulfate of Komai *et al.*, which is used to remove [EDA(+)] fibronectin from the blood of rheumatoid arthritis patients, for the treatment of osteoarthritis as disclosed in Hill *et al.*

Indeed, as discussed above, Komai *et al.* neither teach nor suggest a method for the treatment of osteoarthritis because Komai *et al.* describe "a plasma-separation bilayer gellan-gallansulfate adsorbed for direct removal of extra domain A containing fibronectin from the blood of rheumatoid arthritis patients." The teachings of Komai *et al.* alone are evidence to show that the required therapies for osteoarthritis and for rheumatoid arthritis would be different because the two illnesses are different.

Accordingly, one of ordinary skill in the art would not have been motivated to even try to obtain the presently claimed method for the treatment of osteoarthritis from a treatment for rheumatoid arthritis.

With regard to Cullis-Hill *et al.*, Applicants note that Cullis-Hill *et al.* discloses that polysulphated polysaccharides derived from alginic acid, pectin and inulin (among others) have a variety of biological activities. The most widely studied activities include inhibition of acid and neutral proteinases (e.g. human granulocyte elastase, HGE) and lysosomal hydrolases (e.g.

hyaluronidase), anti-viral (e.g. Herpes Simplex), anti-inflammatory and anti-coagulant activity (column 5, lines 53-64). Cullis-Hill *et al.* also describe that the administration of the compositions is via direct injection (intra-articular administration) (column 8, lines 28-37; and column 8, lines 51-55). As pointed out by the Office Action, Cullis-Hill *et al.* do not exemplify the treatment of osteoarthritis using the polysulphated polysaccharides as presently claimed. In addition, Cullis-Hill *et al.* neither teach nor suggest the use of the polysulphated polysaccharides by oral administration. In fact, Cullis-Hill *et al.* discloses that the preferred method of administration is by direct injection into the damaged tissues, such as for example, into the synovial cavity, and that when the compositions are used at high concentrations, then the compositions may be administered intra-muscularly, subcutaneously, intravenously or topically.

Moreover, Cullis-Hill *et al.* teach away from using polysulphated polysaccharides in the form of a salt of sodium, of potassium or of ammonium, because Cullis-Hill *et al.* state that "the metallo complexes of this class of drugs (polysulphated polysaccharides) were more potent stimulators of proteoglycan synthesis than the sodium salt" (see column 24, lines 1-5 of Cullis-Hill *et al.*) and that "the formation of these metallo-polysulphated polysaccharide complexes provides a useful means of transporting selected metals into bodily tissues, since unlike the known salts of the polysulphated polysaccharides like sodium, potassium, or ammonium, which dissociate into the respective ions when dissolved in water, the complexes of the present invention do not dissociate in an aqueous or physiological media" (see column 11, lines 49-59 of Cullis-Hill *et al.*).

Consequently, Cullis-Hill *et al.* neither teach nor suggest the presently claimed method for the treatment of osteoarthritis comprising administering orally to a mammal in need thereof a therapeutically effective amount of a sulphated polysaccharide in acid form or as a

physiologically acceptable salt thereof, selected from the group consisting of inulin sulphate, gellan sulphate, pullulan sulphate, curdlan sulphate, alginic acid sulphate, laminarin sulphate and pectin sulphate (as well as the corresponding polysulphates).

Thus, Cullis-Hill *et al.* would not have motivated one of ordinary skill in the art at the time the invention was made to use polysulphated polysaccharides for the treatment of osteoarthritis. Moreover, one of ordinary skill in the art would not have been motivated to use the polysulphated polysaccharides in the form of a salt of sodium, potassium or ammonium.

Applicants also submit herewith a Rule 132 Declaration providing an *in vivo* assay to demonstrate the unexpectedly superior effect of orally administered inulin polysulphate for the treatment of osteoarthritis in comparison to orally administered chondroitin sulphate. Specifically, as demonstrated in the results of the *in vivo* assay, the present inventors have shown that the claimed sulphated polysaccharide, inulin polysulphate, is surprisingly more effective than chondroitin sulphate at the same dose.

Furthermore, with regard to the statement at page 8, last paragraph of the present Office Action[3], Applicants respectfully disagree and note the followings four documents (attached herewith) which show that a sulfated glycosaminglycan, namely chondroitin sulphate, as well as

[3] That "one of skill in the art would be motivated to use the active agents in the method of treatment as instantly claimed since they inhibit the release and the action of the serine proteinases. The proteoglycans, which confer the property of resilience of the joints, are depleted due to excessive degradation of proteinases. Hence inhibition of the degradation of the proteinases inhibits the depletion of the proteoglycans, which are needed to maintain the resilience of joints. One of skill in the art would expect the structurally related polysulfated polysaccharides to perform the same functions and would look for other related sulfated polysulfated polysaccharides for use in the method of treatments as instantly claimed."

a glycosaminglycan without any sulfate groups, namely hyaluronic acid, inhibits the synthesis of metalloproteinases and are useful in the treatment of osteoarthritis:

- J. Monfort et al., *Drugs Exptl. Clin. Res.*, XXXI(2):71-76 (2005);
- M.W. Orth et al., *Equine Vet. J., Suppl.*, 34:224-229 (2002);
- A. Sasaki et al., *Tohoku J. Exp. Med.*, 204:99-107 (2004); and
- K. Takahashi et al., *Osteoarthritis and Cartilage*, 7:182-190 (1999),

Thus, contrary to the Office Action's contention, one skilled in the art would not necessarily look for other sulphated polysaccharides since a polysaccharide without any sulphate groups might perform the same functions (see cited documents above).

Reconsideration and withdrawal of the rejection under § 103(a) is respectfully requested.

Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The U.S. Patent and Trademark Office is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,

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